

APPENDIX C:
CLAIMS OF U.S. PATENT NO. 6,869,605
CORRESPONDING TO THE PROPOSED COUNT

6,869,605 Claims	Reason Claim Corresponds to Proposed Count
<p>1. A method of inhibiting B-cell growth in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds human BAFF (SEQ ID NO:1), wherein B-cell growth in the animal is inhibited.</p>	<p>This claim would be anticipated and/or rendered obvious by the Proposed Count because it was well known at the time the invention was made that:</p> <ul style="list-style-type: none"> • the term “B-cell” recited in the claims of the ‘605 Patent is interchangeable with the term “B lymphocyte” recited in the Proposed Count. <i>See, e.g., Janeway, C. & P. Travers. Immunobiology: The Immune System in Health and Disease, (Current Biology Ltd./Garland Publishing, London) 1994; p. 1:8 (legend to Figure 1.7 which uses the terms “B cell” and “B lymphocyte” interchangeably)(Appendix M).</i> Moreover, the equivalence of “B cell” and “B lymphocyte” is readily apparent from reading the ‘605 Patent. For example, column 18 of the ‘605 Patent at lines 55-67, particularly lines 55 and 63 refers to “antigen-specific B lymphocytes” and “antigen-specific B cells” interchangeably. Similarly, column 19 of the ‘605 Patent at lines 1-6, particularly lines 3 and 6, refers to “B lymphocytes” and “B cells” interchangeably. • B lymphocytes, when activated, undergo proliferation (growth) and differentiation (maturation) into antibody producing (immunoglobulin producing) B cells. <i>See, e.g., Janeway, C. & P. Travers. Immunobiology: The Immune System in Health and Disease, (Current Biology Ltd./Garland Publishing, London) 1994; pp. 3:38 and 8:2 (legend to Figure 8.1)(Appendix M); and Abbas, A.K. et al., Cellular and Molecular Immunology, (W.B. Saunders Company, Harcourt Brace Jovanovich, Inc., Philadelphia) 1991; pp. 187 and 189 (Appendix N).</i> Accordingly, the method of inhibiting B lymphocytes in the Proposed Count anticipates and/or renders obvious the methods of inhibiting B-cell growth, maturation and immunoglobulin production recited in the claims of the ‘605 Patent. • the administration of a “therapeutically effective amount” of the recited antibody is the amount sufficient to achieve the desired result;

	<ul style="list-style-type: none"> the amino acid sequence of BAFF (SEQ ID NO:1) of the '605 Patent is identical to the amino acid sequence of the protein recited in the Proposed Count (see Appendix O); and because BAFF and the protein recited in the Proposed Count are the same molecule, an "anti-BAFF antibody that binds human BAFF (SEQ ID NO:1)" is interchangeable with an "an antibody that binds a protein whose amino acid sequence is: MDDSTEREQS RLTSLKKRE EMKLKECVSI LPRKESPSVR SSKDGKLLAA TLLLALLSCC LTVVSYQVA ALQGDLASLR AELQGHHAEK LPAGAGAPKA GLEEAPAVTA GLKIFEPPAP GEGNSSQNSR NKRAVQGPEE TVTQDCLQLI ADSEPTTIQK GSYTFVPWLL SFKRGSALEE KENKILVKET GYFFIYGQVL YTDKTYAMGH LIQRKKVHVF GDELSLVTLF RCIQNMPETL PNNSCYSAGI AKLEEGDELQ LAIPRENAQI SLGDGVTFGG ALKLL". <p>Thus, because all of the limitations recited in Claim 1 of the '605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 1 corresponds to the Proposed Count.</p>
2. A method of inhibiting immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds human BAFF (SEQ ID NO:1), wherein immunoglobulin production in the animal is inhibited.	<p>This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claim 1.</p> <p>Thus, because all of the limitations recited in Claim 2 of the '605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 2 corresponds to the Proposed Count.</p>
3. A method of co-inhibiting B-cell growth and immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds human BAFF (SEQ ID NO:1), wherein B-cell growth and immunoglobulin production in the animal are inhibited.	<p>This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claim 1.</p> <p>Thus, because all of the limitations recited in Claim 3 of the '605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 3 corresponds to the Proposed Count.</p>
4. A method of inhibiting B-cell growth and maturation in an animal comprising the step of administering a therapeutically effective amount of an	<p>This claim would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claim 1.</p>

<p>anti-BAFF antibody that binds human BAFF (SEQ ID NO:1), wherein B-cell growth and maturation in the animal are inhibited.</p>	<p>Thus, because all of the limitations recited in Claim 4 of the ‘605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 4 corresponds to the Proposed Count.</p>
<p>5. A method of inhibiting B-cell growth in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds murine BAFF (SEQ ID NO:2), wherein B-cell growth in the animal is inhibited.</p>	<p>Claim 5 of the ‘605 Patent would be anticipated or rendered obvious by the Proposed Count for the same reasons explained above for Claim 1 and in view of the following comments.</p> <p>During prosecution of the ‘605 Patent, Biogen admitted that an antibody that binds murine BAFF is intended to encompass antibodies that also bind human BAFF. Specifically, in the context of amending a claim to replace the phrase “an antibody specific for BAFF ligand” with “an anti-BAFF ligand that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF”, Biogen argued that “antibodies directed against a protein from one species may, and often do, cross react with orthologs of that protein from other species, particularly if there is a high percent identity with a respective ortholog. Additionally, antibodies against a protein typically also recognize variants of that protein, including, for example, fragments and modified sequences, so long as antigenic determinant(s) remain(s) intact. <i>The claims as amended encompass all such antibodies.</i>” See, Amendment dated January 16, 2004 (Appendix L at page 3, last paragraph bridging to page 4) (emphasis added). This statement makes it clear that “an antibody that binds murine BAFF” is a genus of antibodies that encompasses the antibody recited in the count.</p> <p>Thus, because all of the limitations recited in Claim 5 of the ‘605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 5 corresponds to the Proposed Count.</p>
<p>6. A method of inhibiting immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds murine BAFF (SEQ ID NO:2), wherein immunoglobulin production in the animal is inhibited.</p>	<p>Claim 6 of the ‘605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 2 and 5.</p> <p>Thus, because all of the limitations recited in Claim 6 of the ‘605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 6 corresponds to the Proposed Count.</p>

<p>7. A method of co-inhibiting B-cell growth and immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds murine BAFF (SEQ ID NO:2), wherein B-cell growth and immunoglobulin production in the animal are inhibited.</p>	<p>Claim 7 of the '605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 3 and 5.</p> <p>Thus, because all of the limitations recited in Claim 7 of the '605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 7 corresponds to the Proposed Count.</p>
<p>8. A method of inhibiting B-cell growth and maturation in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody that binds murine BAFF (SEQ ID NO:2); wherein B-cell growth and maturation in the animal are inhibited.</p>	<p>Claim 8 of the '605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 4 and 5.</p> <p>Thus, because all of the limitations recited in Claim 8 of the '605 Patent would either be anticipated or rendered obvious by the Proposed Count, Claim 8 corresponds to the Proposed Count.</p>
<p>9. The method according to any one of claims 1-8, wherein the anti-BAFF antibody is a monoclonal antibody.</p>	<p>Claim 9 of the '605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 1-8, and in addition, because methods of making and using monoclonal antibodies were well known in the art at the time the invention was made, as acknowledged by Biogen in its '605 Patent. <i>See, e.g., '605 Patent, col. 11, lines 4-8</i> ("Antiprotein/anti-peptide antisera or monoclonal antibodies can be made by standard laboratory protocols (See, for example, <i>Antibodies, A Laboratory Manual</i> ed. by Harlow and Lane (Cold Spring Harbor Press: 1988)").</p> <p>Accordingly, it would have been obvious to use the monoclonal antibody of Claim 9 in the recited method in view of the Proposed Count, and therefore Claim 9 corresponds to the Proposed Count.</p>
<p>10. The methods of claim 9, wherein the antibody is recombinantly produced.</p>	<p>Claim 10 of the '605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 1-9 and in addition, because methods of making and using recombinantly produced antibodies, including chimeric antibodies and antibodies comprising human constant domains, were well known in the art at the time the invention was made, as acknowledged by Biogen in its '605 Patent. <i>See, '605 Patent, col. 11, line 66 - col. 12, line 8</i> ("Various forms of antibodies can also be made using standard</p>

	<p>recombinant DNA techniques. Winter and Milstein (1991) <i>Nature</i> 349:293-299, specifically incorporated by reference herein. For example, chimeric antibodies can be constructed in which the antigen binding domain from an animal antibody is linked to a human constant domain (e.g. Cabilly et al., U.S. Pat. No. 4,816,567, incorporated herein by reference). Chimeric antibodies may reduce the observed immunogenic responses elicited by animal antibodies when used in human clinical treatments.”).</p> <p>Accordingly, it would have been obvious to use the recombinantly produced monoclonal antibody of Claim 10 in the recited method in view of the Proposed Count, and therefore Claim 10 corresponds to the Proposed Count.</p>
<p>11. The method as in claim 9, wherein the antibody is a chimeric antibody.</p>	<p>Claim 11 of the ‘605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 1-10.</p> <p>Accordingly, it would have been obvious to use the chimeric monoclonal antibody of Claim 11 in the recited method in view of the Proposed Count, and therefore, Claim 11 corresponds to the Proposed Count.</p>
<p>12. The method as in claim 9, wherein the antibody is a humanized antibody.</p>	<p>Claim 12 of the ‘605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 1-9, and in addition, because methods of making and using humanized antibodies were well known in the art at the time the invention was made, as acknowledged by Biogen in its ‘605 Patent. <i>See, ‘605 Patent, col. 12, lines 9-24</i> (“In addition, recombinant ‘humanized antibodies’ which recognize BAFF-ligand or its receptors can be synthesized. Humanized antibodies are chimeras comprising mostly human IgG sequences into which the regions responsible for specific antigen-binding have been inserted. Animals are immunized with the desired antigen, the corresponding antibodies are isolated, and the portion of the variable region sequences responsible for specific antigen binding are removed. The animal-derived antigen binding regions are then cloned into appropriate position of human antibody genes in which the antigen binding regions have been deleted. Humanized antibodies minimize the use of heterologous (i.e. inter species) sequences in human antibodies, and</p>

	<p>thus are less likely to elicit immune responses in the treated subject.”)</p> <p>Accordingly, it would have been obvious to use the humanized monoclonal antibody of Claim 12 in the recited method in view of the Proposed Count, and therefore Claim 12 corresponds to the Proposed Count.</p>
<p>13. The method as in claim 9, wherein the antibody comprises human constant domains.</p>	<p>Claim 13 of the ‘605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained for Claims 1-10.</p> <p>Accordingly, it would have been obvious to use the monoclonal antibody comprising human constant domains of Claim 13 in the recited method in view of the Proposed Count, and therefore, Claim 13 corresponds to the Proposed Count.</p>
<p>14. The method as in claim 9, wherein the antibody is a F(ab')₂ fragment.</p>	<p>Claim 14 of the ‘605 Patent would be anticipated and/or rendered obvious by the Proposed Count for the same reasons explained above for Claims 1-9, and in addition, because methods of making and using F(ab')₂ fragments were well known in the art at the time the invention was made, as acknowledged by Biogen. <i>See, ‘605 Patent, col. 11, lines 50-56</i> (“The term antibody was used herein is intended to include fragments thereof which are also specifically reactive with BAFF-ligand, or its receptors. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, F(ab')₂ fragments can be generated by treating antibody with pepsin.”)</p> <p>Accordingly, it would have been obvious to use the monoclonal antibody that is an F(ab')₂ fragment of Claim 14 in the recited method in view of the Proposed Count, and therefore, Claim 14 corresponds to the Proposed Count.</p>